



DEPARTMENT OF THE AIR FORCE
59TH MEDICAL WING (AETC)
JOINT BASE SAN ANTONIO - LACKLAND TEXAS



15 JUNE 2017

MEMORANDUM FOR SGVT

ATTN: CAPT KELSEY A CACIC

FROM: 59 MDW/SGVU

SUBJECT: Professional Presentation Approval

1. Your paper, entitled **Concentrations of Serum Inflammatory Markers after Hypobaric Exposure in Aircrew Trainees** presented at/published to **MHSRS, Kissimmee, FL, 27-30 Aug 2017** in accordance with MDWI 41-108, has been approved and assigned local file #17264.
2. Pertinent biographic information (name of author(s) title, etc.) has been entered into our computer file. Please advise us (by phone or mail) that your presentation was given. At that time, we will need the date (month, day and year) along with the location of your presentation. It is important to update this information so that we can provide quality support for you, your department, and the Medical Center commander. This information is used to document the scholarly activities of our professional staff and students, which is an essential component of Wilford Hall Ambulatory Surgical Center (WHASC) internship and residency programs.
3. Please know that if you are a Graduate Health Sciences Education student and your department has told you they cannot fund your publication, the 59th Clinical Research Division may pay for your basic journal publishing charges (to include costs for tables and black and white photos). We cannot pay for reprints. If you are a 59 MDW staff member, we can forward your request for funds to the designated Wing POC at the Chief Scientist's Office, Ms. Alice Houy, office phone: 210-292-8029; email address: alice.houy.civ@mail.mil.
4. Congratulations, and thank you for your efforts and time. Your contributions are vital to the medical mission. We look forward to assisting you in your future publication/presentation efforts.

Linda Steel-Goodwin

LINDA STEEL-GOODWIN, Col, USAF, BSC
Director, Clinical Investigations & Research Support

PROCESSING OF PROFESSIONAL MEDICAL RESEARCH/TECHNICAL PUBLICATIONS/PRESENTATIONS

INSTRUCTIONS

USE ONLY THE MOST CURRENT 59 MDW FORM 3039 LOCATED ON AF E-PUBLISHING

1. The author must complete page two of this form:
 - a. In Section 2, add the funding source for your study [e.g., 59 MDW CRD Graduate Health Sciences Education (GHSE) (SG5 O&M); SG5 R&D; Tri-Service Nursing Research Program (TSNRP); Defense Medical Research & Development Program (DMRDP); NIH; Congressionally Directed Medical Research Program (CDMRP) ; Grants; etc.]
 - b. In Section 2, there may be funding available for journal costs, if your department is not paying for figures, tables or photographs for your publication. Please state "YES" or "NO" in Section 2 of the form, if you need publication funding support.
2. Print your name, rank/grade, sign and date the form in the author's signature block or use an electronic signature.
3. Attach a copy of the 59 MDW IRB or IACUC approval letter for the research related study. If this is a technical publication/presentation, state the type (e.g. case report, QA/QI study, program evaluation study, informational report/briefing, etc.) in the "Protocol Title" box.
4. Attach a copy of your abstract, paper, poster and other supporting documentation.
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8. The 59 CRD/Publications and Presentations Section will route the request form to clinical investigations, 502 ISG/JAC (Ethics Review) and Public Affairs (59 MDW/PA) for review and then forward you a final letter of approval or disapproval.
9. Once your manuscript, poster or presentation has been approved for a one-time public release, you may proceed with your publication or presentation submission activities, as stated on this form. **Note:** For each new release of medical research or technical information as a publication/presentation, a new 59 MDW Form 3039 must be submitted for review and approval.
10. If your manuscript is accepted for scientific publication, please contact the 59 CRD/Publications and Presentations Section at 292-7141. This information is reported to the 59 MDW/CC. All medical research or technical information publications/presentations must be reported to the Defense Technical Information Center (DTIC). See 59 MDWI 41-108, *Presentation and Publication of Medical and Technical Papers*, for additional information.
11. The Joint Ethics Regulation (JER) DoD 5500.07-R, *Standards of Conduct*, provides standards of ethical conduct for all DoD personnel and their interactions with other non-DoD entities, organizations, societies, conferences, etc. Part of the Form 3039 review and approval process includes a legal ethics review to address any potential conflicts related to DoD personnel participating in non-DoD sponsored conferences, professional meetings, publication/presentation disclosures to domestic and foreign audiences, DoD personnel accepting non-DoD contributions, awards, honoraria, gifts, etc. The specific circumstances for your presentation will determine whether a legal review is necessary. **If you (as the author) or your supervisor check "NO" in block 17 of the Form 3039, your research or technical documents will not be forwarded to the 502 ISG/JAC legal office for an ethics review.** To assist you in making this decision about whether to request a legal review, the following examples are provided as a guideline:

For presentations before professional societies and like organizations, the 59 MDW Public Affairs Office (PAO) will provide the needed review to ensure proper disclaimers are included and the subject matter of the presentation does not create any cause for DoD concern.

If the sponsor of a conference or meeting is a DoD entity, an ethics review of your presentation is not required, since the DoD entity is responsible to obtain all approvals for the event.

If the sponsor of a conference or meeting is a non-DoD commercial entity or an entity seeking to do business with the government, then your presentation should have an ethics review.

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If you are receiving an honorarium or payment for speaking, a legal ethics review is required.

If you (as the author) or your supervisor check "YES" in block 17 of the Form 3039, your research or technical documents will be forwarded simultaneously to the 502 ISG/JAC legal office and PAO for review to help reduce turn-around time. If you have any questions regarding legal reviews, please contact the legal office at (210) 671-5795/3365, DSN 473.

NOTE: All abstracts, papers, posters, etc., should contain the following disclaimer statement:

"The views expressed are those of the [author(s)] [presenter(s)] and do not reflect the official views or policy of the Department of Defense or its Components"

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"The voluntary, fully informed consent of the subjects used in this research was obtained as required by 32 CFR 219 and DODI 3216.02_AFI 40-402."

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"The experiments reported herein were conducted according to the principles set forth in the National Institute of Health Publication No. 80-23, Guide for the Care and Use of Laboratory Animals and the Animal Welfare Act of 1966, as amended."

PROCESSING OF PROFESSIONAL MEDICAL RESEARCH/TECHNICAL PUBLICATIONS/PRESENTATIONS			
1. TO: CLINICAL RESEARCH	2. FROM: (Author's Name, Rank, Grade, Office Symbol) Kelsey A. Cacic, 03, SGVT	3. GME/GHSE STUDENT: <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO	4. PROTOCOL NUMBER: FWH20140087H
5. PROTOCOL TITLE: (NOTE: For each new release of medical research or technical information as a publication/presentation, a new 59 MDW Form 3039 must be submitted for review and approval.) MRI Following Single Exposure to Hypobaria and/or Hypoxia Protocol			
6. TITLE OF MATERIAL TO BE PUBLISHED OR PRESENTED: Concentrations of Serum Inflammatory Markers after Hypobaric Exposure in Aircrew Trainees			
7. FUNDING RECEIVED FOR THIS STUDY? <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO FUNDING SOURCE: AFMS RDT&E			
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16. AUTHORSHIP AND CO-AUTHOR(S) List in the order they will appear in the manuscript.			
LAST NAME, FIRST NAME AND M.I.	GRADE/RANK	SQUADRON/GROUP/OFFICE SYMBOL	INSTITUTION (If not 59 MDW)
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c. Sherman, Paul	06	USAF School of Aerospace Medicine	Wright-Patterson
d. McGuire, Steven	RETIRED	59 MDW & USAFSAM	
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21. APPROVING AUTHORITY'S PRINTED NAME, RANK, TITLE JEFFREY C. McCLEAN, Lt Col, Neurology Program Director		22. APPROVING AUTHORITY'S SIGNATURE MCCLEAN.JEFFREY.C.11.1022417343	23. DATE 12Jun2017

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28. AUTHOR CONTACTED FOR RECOMMENDED OR NECESSARY CHANGES: <input type="checkbox"/> NO <input checked="" type="checkbox"/> YES If yes, give date. 14 Jun 2017 <input type="checkbox"/> N/A		
29. COMMENTS <input checked="" type="checkbox"/> APPROVED <input type="checkbox"/> DISAPPROVED The author added the human research disclaimer statement to the poster presentation and provided the IRB approval letter for the research study. The poster presentation is approved.		
30. PRINTED NAME, RANK/GRADE, TITLE OF REVIEWER Rocky Calcote, PhD, Clinical Research Administrator	31. REVIEWER SIGNATURE CALCOTE.ROCKY.D.1178245844 <small>Digitaly signed by CALCOTE.ROCKY.D.1178245844 DN: cn=US, ou=U.S. Government, ou=DoD, ou=PMI, ou=USAP, email=CALCOTE.ROCKY.D.1178245844 Date: 2017.06.15 08:15:43 -0500</small>	32. DATE June 15, 2017
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42. PRINTED NAME, RANK/GRADE, TITLE OF REVIEWER Kevin Iinuma, SSgt/E-5, 59 MDW Public Affairs	43. REVIEWER SIGNATURE IINUMA.KEVIN.MITSUGU.1296227 <small>Digitaly signed by IINUMA.KEVIN.MITSUGU.1296227 DN: cn=US, ou=U.S. Government, ou=DoD, ou=PMI, ou=USAP, email=IINUMA.KEVIN.MITSUGU.1296227 Date: 2017.06.15 08:17:44 -0500</small>	44. DATE June 15, 2017
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Concentrations of Serum Inflammatory Markers after Hypobaric Exposure in Aircrew Trainees

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BACKGROUND

Recurrent non-hypoxic hypobaric exposure in Air Force U-2 pilots is associated with acquired decrements in neurocognitive performance with parallel diffuse axonal injury demonstrated on magnetic resonance imaging (MRI). The pathophysiology of this brain injury is not well understood but may be related to quantitative changes in inflammatory serum markers.^{1,2} The aim of this study is to assess whether protein and cytokine concentrations change after non-hypoxic hypobaric exposure. We hypothesized that inflammatory markers, which elevate in decompression sickness, traumatic brain injury (TBI), and various neurological conditions associated with decreased neurocognitive performance, would change in response to hypobaric exposure.

SERUM MARKERS

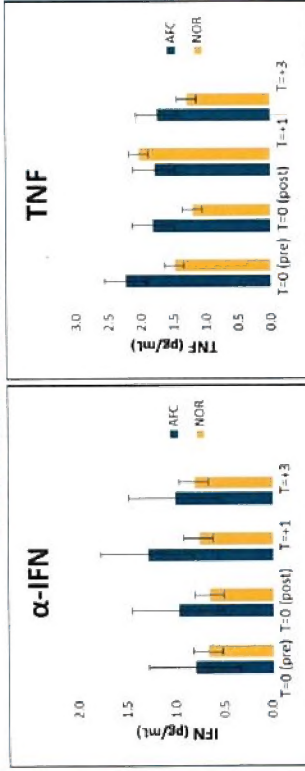
α-IFN: Biomarker of neuro-inflammation
TNF: Higher levels after TBI have been correlated with more severe injuries³
IL-6: Cytokine, seen elevated after severe TBI and subarachnoid hemorrhage^{3,5}
SB-100: S-100 calcium binding protein B, elevate with hypoxic hypobaric injury,⁶ increase with greater injury severity and decreased survival⁷

METHODS

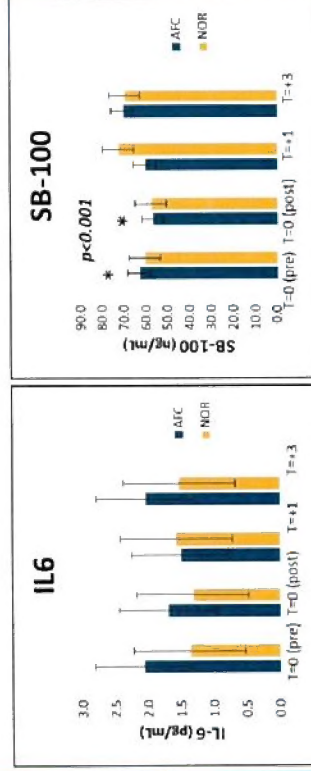
Subjects: 75 aircrew trainees (AFC) and 50 controls (NOR) matched for age, health, and physical activity levels
Exposure: Aircrew chamber training: 100% O₂ @ 25,000 ft at 4.5 psi; approximately 30 min hypobaric, 2-5 min hypoxic
Data Collection: Serum was collected 30 min before, 30 min after, 24 h, 72 h in relation to exposure
Analysis: Within-group two-tailed paired t-test between time points

RESULTS

Concentrations of serum markers



Error bars: confidence intervals with alpha 0.05.



Error bars: confidence intervals with alpha 0.05.

Within-group two-tailed paired t-test analysis demonstrated a decrease in SB-100 in the exposure group from pre-hypobaric exposure to post-hypobaric exposure without significant change 24 h or 72 h after exposure. There were no statistically significant differences in α -IFN, TNF, or IL-6 concentrations compared to baseline at any time points.

CONCLUSION

This study provides evidence of inflammatory marker changes in serum SB-100 concentrations without clinical symptoms, demonstrating possible secondary response to hypobaric exposure. Prior research has demonstrated SB-100 involvement with blood-brain barrier regulation, an etiology that is thought to be involved in hypobaric-induced pathophysiology.⁶ SB-100 has also received recent attention as a biomarker for TBI associated with cell division, apoptosis, and inflammation.⁷ Changes in SB-100 after hypobaric exposure may help explain the pathophysiology for the pattern of damage seen on imaging. Limitations of this study include clinical lab analysis; further analyses will be conducted in a research lab. Further research is needed to elucidate involvement of other inflammatory cytokines and effects of repeated non-hypoxic hypobaric exposure.

FUTURE DIRECTIONS

Phase 3 Single Exposure Human
Consider additional biomarkers
Phase 3 Recurrent Exposure (Swine)
CSF and serum biomarkers
U-2 pilot occupational MRI



BIBLIOGRAPHY

1. Ozer A, Erbilgin M, Metinler M, et al. Multiplexed bead-based assay to characterize different inflammatory cytokines in posttraumatic and other diseases. *Neurology*. 2016; 86:56-67.
2. Song TG, Wu JH, Guo YQ, et al. Systemic pro-inflammatory response facilitates the development of cerebral ischemia during stroke injury. *J Neuroinflammation*. 2016; 13:261-83.
3. Ozer A, Erbilgin M, Metinler M, et al. Inflammatory role of pro-inflammatory cytokines after traumatic brain injury. *Brain*. 2016; 139:1504-1515.
4. Kumar R, Rubin R, Wang JY, Ischakova PM, Wager AC. Principal components derived from CSF inflammatory profiles predict outcomes in survivors after severe traumatic brain injury. *Brain*. 2016; 139:183-193.
5. Neme A, Oskur A, Nakata T, Matsuo K, Yoshida T, Yamaguchi M, Iwakura M, Kudo T, et al. IL-25, a Th17-inducing cytokine, exacerbates neuroinflammation and neuronal damage in a murine model of traumatic brain injury. *J Neurosci*. 2012; 32:1317-327.
6. Wornat G, Ninkovic J, Cardinale J, Perny A, Billard M. The response to lipopolysaccharide brain injury of high altitude plateau (3500m) levels and the possible effect of acclimatization on blood brain barrier dysfunction. *Neurosci Lett*. 2016; 617:451-458.
7. Ozer A, Erbilgin M, Metinler M, et al. IL-100 concentrations are a predictor of decreased survival in patients with severe traumatic brain injury. *Int J Surg*. 2016; 32:193-202.

The views expressed are those of the authors and do not necessarily reflect the official policy or position of Brooke Army Medical Center, the U.S. Army Medical Department, the U.S. Army Office of the Surgeon General, the U.S. Army, the U.S. Air Force, the Department of Defense, or the Department of Health and Human Services. This research was obtained as required by 32 CFR 219 and DODI 3216.02 AF140-402.

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